PREVALENCE OF HEPATOPULMONARY SYNDROME IN CIRRHOSIS PATIENTS

Dissertation submitted for

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Chennai, Tamilnadu.

CERTIFICATE

This is to certify that this dissertation titled **"PREVALENCE OF HEPATO PULMONARY SYNDROME IN CIRRHOSIS PATIENTS"** submitted by Dr. R. SANKAR to the faculty of General Medicine, The Tamilnadu Dr. M.G.R. Medical University, and Chennai in partial fulfillment of the requirement for the award of MD degree Branch I (General Medicine) is a bonafide research work carried out by him under our direct supervision and guidance.

Dr.S.VADIVEL MURUGAN.M.D

Additional Professor,
Department of Medicine,
Madurai Medical College,
Madurai.

Dr.AYYAPPAN.M.D

Professor and Head,
Department of Medicine,
Madurai Medical College,
Madurai.

Place: Madurai
Date:

DECLARATION

I, Dr. R.SANKAR, solemnly declare that the dissertation titled **"PREVALENCE OF HEPATOPULMONARY SYNDROME IN CIRRHOSIS PATIENTS"** has been prepared by me.

This is submitted to the Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfillment of the regulations for the award of MD Degree Branch I (General Medicine).

It was not submitted to the award of any degree/ diploma to any University either in part or in full form previously.

Place : Madurai

Date :

Dr. R.SANKAR

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ABBREVATIONS AND ACRONYMS

HPS – Hepato pulmonary syndrome

IPVDS – Intrapulmonary vascular dilatation syndrome

PaO2 – Partial pressure of oxygen

MAA – Macro aggregated albumin

Hb – Haemoglobin

TC – Total count

DC – Differntial count

ECG – Electrocardiography

ABG – Arterial blood gas analysis

OGD – Oesophago gastro duodenoscopy

CEE – Contrast enhanced echocardiography

CONTENTS

INTRODUCTION

Hepatopulmonary syndrome (HPS) is said to exist when a combination of the following

three are present:

1) Evidence of chronic liver disease complicated by portal hypertension (With or without cirrhosis),
2) Arterial hypoxemia with partial pressure of oxygen (PaO2) in arterial blood <80 mmHg or alveolar-arterial (A-a) oxygen gradient >20 mmHg
3) Intrapulmonary vascular dilatations documented on contrast enhanced echocardiography or technetium99m labeled albumin scanning.

Some patients with intrapulmonary vascular dilatations may not develop hypoxemia and is referred to as intrapulmonary vascular dilatation syndrome (IPVDS) or sub-clinical HPS.

The predominant abnormality identified are intrapulmonary vascular dilatations (IPVDs), occurring at capillary and precapillary levels and these serve as functional shunts.

Anatomic arteriovenous anastomoses, pleural spider naevi, ventilation perfusion abnormalities, impaired hypoxic pulmonary vasoconstriction and portopulmonary vascular shunts are known to contribute. **Evidence till date suggests that shunting of blood through IPVDs is the most important cause of hypoxemia in HPS**, and like other functional shunts it responds to supplemental oxygen. Two-dimensional transthoracic echocardiography using agitated saline or indocyanine green as contrast is the most commonly used method for identifying these shunts.

REVIEW OF LITERATURE

Hypoxemia is a common clinical manifestation in patients with liver cirrhosis. It may result from the common cardiopulmonary diseases such as pneumonia, chronic obstructive pulmonary disease, congestive heart failure and pulmonary edema.

A relationship between cirrhotic liver and lung was first described by Fluckiger[1] in 1884 based on the observation of a woman with cirrhosis, cyanosis and clubbed digits. Several authors have since confirmed this finding. In 1977, Kennedy and Knudson coined the term "hepatopulmonary syndrome" to describe this entity[2]. Although more prevalent in patients with cirrhosis, HPS has also been reported in association with other liver diseases like the Budd-Chiari syndrome and schistosomiasis.

Further, HPS has been reported in non cirrhotic portal hypertension, suggesting thereby that portal hypertension may play a role in the pathogenesis independent of liver dysfunction. A study from Calcutta mentioned an occurrence of 9.5% in patients with non cirrhotic portal fibrosis, a condition with essentially normal liver function. In the light of this evidence, the criteria for HPS need to be modified to a triad of portal hypertension, hypoxemia and intrapulmonary vascular dilatations, and it would be more appropriate to term it the "portopulmonary syndrome".

Definition and Demographics

Hepatopulmonary syndrome (HPS) is characterized by the triad of advanced liver disease, arterial hypoxemia (arterial oxygen tension, PaO2 < 80 mmHg or alveolar arterial oxygen gradient > 20 mmHg at room air), and intrapulmonary vascular dilatation[3-5]. The prevalence in the setting of cirrhosis ranges from 4% to 17%[6-8].

The correlation between the severity of liver disease and the existence of HPS remains controversial. One prevailing concept is that the development of intrapulmonary vascular dilatation is related to the progression of liver dysfunction and correlates with systemic vasodilatation and hyperdynamic circulation[9].

In a prospective study, Vachiery et al[10] suggested that cirrhotic patients with HPS were characterized by a higher Child-Pugh's score and a higher hepatic venous pressure gradient. However, other studies did not support this finding[11, 12]. There may be factors other than the severity of liver disease that are important for the development of HPS.

Mechanisms of Hypoxemia

The increased cardiac output and IPVD are thought to be important factors in the development of the HPS. Patients with liver cirrhosis and the HIPS have increased cardiac output of about 7L/min. About 20% to 70% of this is conducted by the IPVD resulting in a short transit time for the blood in the lungs. When breathing a normal room air, the 0_2 drive is enough to oxygenate the red blood cells at the center of the normal pulmonary vessels

In patients with the HPS who have dilated capillaries oxygen molecules from adjacent alveoli cannot diffuse to oxygenate hemoglobin in erythrocytes at the center stream of venous blood. This inadequate oxygenation is enhanced by the short transit time of the hyperdynamic circulation, which does not provide the red blood cells enough time in contact with the alveoli to acquire good amount of oxygen.

When such a patient is in the upright position a disproportionately larger amount of the blood in the pulmonary circulation preferentially flows to the dilated vessels in the hypoventilated lung bases. This further enhances diffusionperfusion impairment leading to platypnea and orthodeoxia. Unlike

what occurs in true anatomical shunts, supplemental oxygen provides enough driving pressure to partially overcome the relative diffusion defect in HPS.

Exercising patients with cirrhosis or HPS while breathing room air or 100% oxygen had caused further impairment of oxygenation, development of wider alveolo-arterial oxygen gradient and larger shunt fraction. This may be explained at least in part, by the shortened transit time. The effect of exercise is more pronounced in patients with the HPS who already demonstrate a severe reduction in aerobic capacity beyond the levels seen in cirrhotics without the syndrome

Normal pulmonary vascular tone is essential for maintaining adequate ventilation / perfusion equation that maintain normal oxygenation. A high or low tone disturbs the equation and leads to hypoxemia. Although the IPVD causing diffusion-perfusion impairment is considered to be the most important factor underlying impaired gas exchange and resulting in severe hypoxemia characteristic of the HPS, it is not enough alone to diagnose HPS as it may not be associated with severe hypoxemia.

Hypoxemic pulmonary vasoconstriction has a fundamental role in maintaining normoxemia by diverting blood away from hypoventilated areas in the

lungs; impairment of this pulmonary vasoconstriction in response to hypoxemia by an unknown mechanism - is hypothesized to be the third element precipitating the HPS .

Pathogenesis

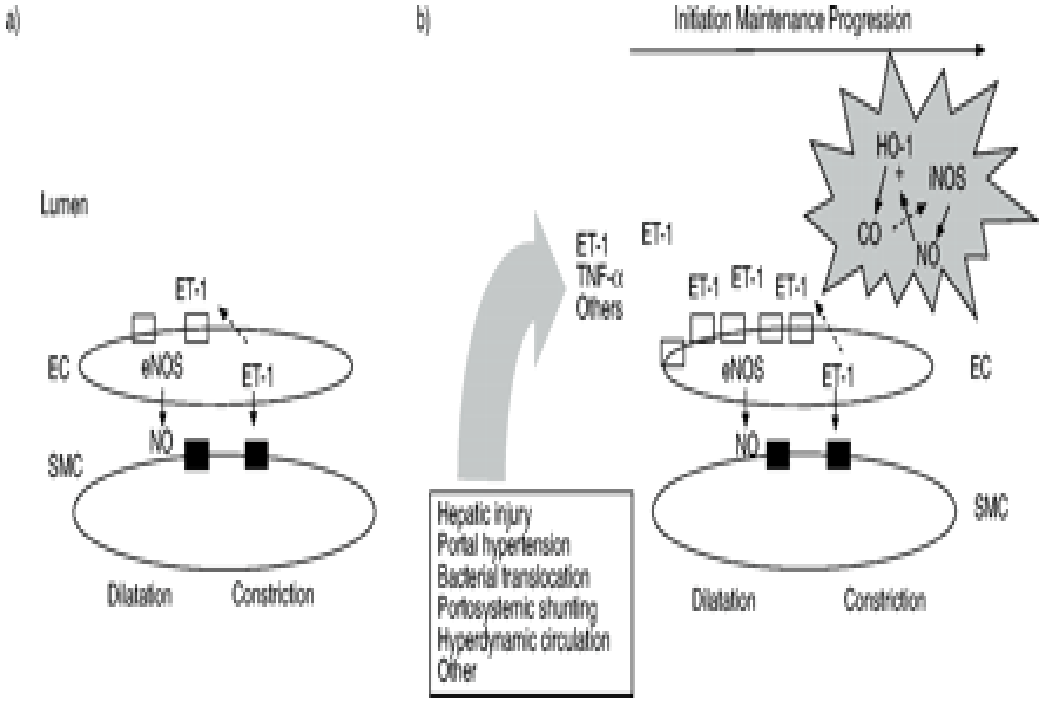


Fig. 1.— Working model of molecular alterations in the pulmonary microcirculation in experimental hepatopulmonary syndrome (HPS).

a) In the normal microvasculature, a balance of vasoconstrictive and vasodilatory factors, including paracrine endothelin (ET)-1-mediated vasoconstriction through the ET_A receptor on smooth muscle cells (SMCs) and ET-1-mediated vasodilatation

mediated through the ET_B receptor linked to endothelial nitric oxide synthase (eNOS) in endothelial cells (ECs), maintain tone.

b) During the development of HPS, a number of alterations, both directly and indirectly relatedto hepatic injury and portal hypertension result in the production or release of mediators into the venous circulation, where they influence the pulmonary microcirculation. Increased expression of pulmonary endothelial ET_B receptors and increased hepatic production and release of ET-1 contribute to an increase in eNOS expression and enhanced nitric oxide (NO) production in the microvascular endothelium during the initiation of HPS. Tumour necrosis factor (TNF)-α-mediated accumulation of intravascular macrophage-like cells also occurs after chronic common bile duct ligation. Haem oxygenase (HO)-1 and inducible nitric oxide synthase (iNOS) expression increase in these cells and contribute to the progression of HPS. CO: carbon monoxide.

The exact pathogenesis of HPS is not completely understood. Common bile duct ligation (CBDL) in rat is the only recognized model for the study of HPS[13]. It is interesting to note that in the animal model of partial portal vein ligation (a model of portal hypertension but without cirrhosis), in which the rats develop a similar degree of portal hypertension and hyper dynamic circulation as CBDL rats, there is no detectable alteration of the pulmonary vasculature[14-16]. Therefore, it is possible that both hepatic injury and portal hypertension are required for the development of HPS.

Castro and Krowka[5] proposed that an imbalance between vasoconstrictors and vasodilators in the pulmonary vasculature contributed to the pathogenesis of HPS. The most extensively investigated vasodilator is nitric oxide (NO). Increased levels of exhaled nitrite and nitrate, the metabolites of NO, are found in patients with HPS; levels return to normal after liver transplantation, with normalization of oxygen saturation. In rats that develop HPS, the level of endothelial NO synthase (eNOS) protein is increased in the region of pulmonary of iNOS in HPS cannot be completely ruled out.

In addition to NO, other vasoactive substances have also been suggested to play a role in the development of HPS. Increased hepatic expression and plasma levels of endothelin-1 (ET-1) have been observed in both experimental and human cirrhosis.

Luo et al[15]reported that increased ET-1 production correlated with intrapulmonary molecular and gas exchange abnormalities, and suggested that ET-1 may contribute to the pathogenesis of HPS.

Thereafter, the same group of investigators also found increased endothelin B (ETB) receptor expression in the pulmonary vasculature from cirrhotic animals. It is known that ET-1 may exert an autocrine vasodilatory effect by

increasing eNOS activity and subsequent NO production via the ETB receptors on vascular endothelial cells.

Accordingly, Luo et al[15] suggested that, in response to the increased circulating ET-1 level in cirrhosis, an increase in pulmonary vascular ETB receptors may result in increased eNOS activity and NO production, with subsequent intrapulmonary vasodilatation. The factors that contribute to increased ETB receptor expression in pulmonary vasculature in cirrhotics have not been completely established.

Hyper dynamic circulation-related increase in pulmonary blood flow with a flow-mediated alteration in vascular ETB receptor expression may play a role. Other factors such as increased cytokine production, particularly of interleukin-1, and hypoxia that are known to alter in cirrhosis may also modulate intrapulmonary ETB receptor expression[26, 27].

Carbon monoxide (CO) is another vasoactive substance that has recently been evaluated for its role in the pathogenesis of HPS[28]. CO can cause vasodilatation by the cyclic guanosine monophosphate (cGMP) independent pathway, possibly by directly activating KCa channels[29]. CO is generated during the degradation of heme by heme oxygenase (HO), which has constitutive and inducible isoforms. HO-1 is an

inducible protein that is expressed in a number of cell types in the lung, most notably alveolar, bronchial epithelium and inflammatory cells, including macrophages.

Increased NO production in cirrhosis has been shown to induce up regulation of intrapulmonaryHO-1 expression, which may be involved in the pathogenesis of HPS. Zhang et al[31] reported that increased CO production induced by pulmonary HO-1 over expression in cirrhotic rats may contribute to the progression of HPS. They also suggested that the increase in pulmonary HO-1 protein may be caused by the accumulation of intravascular macrophages in the early stage after bile duct ligation when cirrhosis and hemodynamic changes have not completely developed. Thereafter, increased CO production can be observed with the development of HPS to worsen gas exchange. However, the mechanism of macrophage accumulation in the pulmonary vasculature is not understood. Increased circulating tumor necrosis factor may be an important triggering factor[31, 32].

Clinical Manifestations

Since intrapulmonary vascular dilatation leads to ventilation-perfusion mismatch, the major clinical manifestation of HPS is impaired oxygenation, which varies from a mild increase in the alveolar-arterial oxygen gradient to severe arterial hypoxemia.

As the vascular abnormalities predominate in the middle to lower lung fields, gravitational effects may increase the blood flow to worsen the ventilation-perfusion mismatch and, finally, result in deterioration in arterial oxygenation when in the upright position. Orthodeoxia, defined as arterial deoxygenation accentuated in the upright position versus the supine position, is a characteristic feature of HPS.

A cutoff value for Orthodeoxia is defined by a PaO2 decrease of 5% or more or 4 mmHg or more from the supine to upright position. Its reported prevalence ranges from 20% to 80% in patients with HPS. Krowka and Cortese[36] found that the mean drop in PaO2 was 12 mmHg when patients stood from the supine position.

Clubbed fingers are common, and the presence of spider nevi has been suggested as one of the most sensitive clinical markers. In cirrhotic patients with portal hypertension, spider nevi, clubbed fingers and hypoxemia are highly suggestive of HPS.

Diagnosis

Several causes other than HPS may be involved in cirrhosis presenting with hypoxemia, such as intrinsic cardiopulmonary abnormalities, pulmonary atelectasis, pneumonia, ascites, pulmonary edema or hepatic hydrothorax.

In cirrhotic patients with clinical symptoms and arterial blood gas compatible with hypoxemia, a chest film must first be taken to rule out reversible conditions. Pulmonary function test should be performed to rule out the common intrinsic pulmonary disorders such as chronic obstructive pulmonary disease. HPS should be suspected in patients who have persistent hypoxia after a normal chest film or after optimal treatment of the underlying conditions.

Contrast enhanced echocardiography is the preferred screening test for HPS. It uses agitated saline or indocyanine green to produce micro bubbles at least 15 μm in diameters that are then injected intravenously. Under normal circumstances, these micro bubbles are trapped in the pulmonary microvasculature and then absorbed. In patients with intracardiac or intrapulmonary shunting, these micro bubbles are seen in the left heart.

Differentiation between intracardiac and intrapulmonary shunting is based on the timing of when these bubbles are found in the left heart. In intracardiac right-to-left shunts, these bubbles appear in the left heart in 3 heartbeats after they appear in the right heart. In intrapulmonary shunts, these bubbles appear in 4–6 heartbeats.

A recent study by Vedrinne et al[37]revealed that transesophageal echocardiography is more sensitive than transthoracic echocardiography in demonstrating intrapulmonary shunting.

However, there are several shortcomings of contrast enhanced echocardiography. First, it cannot quantify the shunting. Second, it cannot differentiate between intrapulmonary vascular dilatation and direct arteriovenous communication. Third, even though contrast echocardiography is highly sensitive for HPS, it lacks specificity.

Proportions of cirrhotic patients with positive results on contrast echocardiography have normal arterial blood gas and do not fulfill the diagnostic criteria for HPS. Lastly, in patients with concomitant intrinsic lung diseases, the contribution of HPS to arterial desaturation cannot be defined by contrast echocardiography.

In order to overcome the disadvantages of contrast echocardiography, the role of 99mtechnetium macro aggregated albumin (Tc-99m MAA) lung perfusion scan in diagnosing HPS was assessed. The albumin macroaggregates are more than 20 μm in diameter. Under normal circumstances, they are entrapped in the pulmonary vasculature. In patients with intracardiac or intrapulmonary shunts, these albumin

macroaggregates can escape the pulmonary vasculature and be taken up by other organs. In normal healthy patients, less than 5% of isotope can be quantified in the brain.

In HPS patients, the fraction is more than 6%. In a cohort study, Tc-99m MAA lung perfusion scan identified all cirrhotic patients with HPS who presented with moderate to severe hypoxemia, and yielded negative results in those without HPS and in all non-cirrhotic hypoxic patients with intrinsic lung disease. Accordingly, Tc-99m MAA scan may be useful for the diagnosis of HPS.

In cirrhotic patients with concomitant intrinsic pulmonary disorders, the fraction of Tc-99m MAA scan can define the significance of the HPS in clinical hypoxemia. That study also showed an inverse correlation between the magnitude of the shunt fraction and arterial oxygen saturation.

The major disadvantage of Tc-99m MAA scan is that it cannot differentiate intracardiac from intrapulmonary shunting. The shunt fraction of Tc-99m MAA scan also does not correlate with the response of PaO2 after 100% oxygen is supplied.

Pulmonary angiography is an invasive procedure that can show the appearance of the pulmonary vasculature. A pulmonary arteriography study in patients

with HPS revealed 2 vascular patterns, the type I or diffuse pattern and the type II or focal pattern.

The minimal diffuse type I pattern is characterized by the presence of normal vessels or finely diffuse spidery vascular abnormalities. The advanced type I pattern is characterized by a diffuse spongy or blotchy appearance.

The type II pattern is a less frequent finding. Patients with advanced type I or type II patterns show a poor response to 100% oxygen. Due to the focal involvement of the pulmonary vasculature and poor treatment response, patients with a type II pattern should be considered for embolization therapy.

Pulmonary angiography should, because of its invasiveness, only be reserved for patients with HPS who respond poorly to 100% inspired oxygen and in whom vascular embolotherapy can be performed at the same time to obliterate the arteriovenous communications.

CT- Scan: It is used for finding other disease processes which cause hypoxemia. However, in HPS, CT scanning of lungs may show dilatation of peripheral pulmonary vasculature.

Treatment and Prognosis

As the major clinical manifestation of HPS is arterial hypoxemia, supplying oxygen is the first line of therapy. Similar to oxygen therapy in patients with chronic obstructive pulmonary disease, long-term oxygen supply prolongs survival in patients with HPS. In patients with poor response to 100% oxygen, pulmonary angiography with embolization therapy is an alternative.

Several medical treatments including almitrine bismesylate, indomethacin, tamoxifen, somatostatin analogues, sympathomimetics, ß-blockers, Methylene blue and plasma exchange have been used in the treatment of HPS with disappointing results[5, 12, 40].

Small series have reported beneficial responses to pharmacological agents such as almitrine,methylene blue,and even garlic powder (Allium sativum), which increase pulmonary vascular resistance, pulmonary artery pressures, and arterial oxygenation. Indomethacin is used with the logic of inhibition of prostaglandin production which has a putative role of vasodilatation. The results of research about indomethacin have been inconclusive.

Methylene blue is a potent inhibitor of NO and its intracellular mediator, gunaylate cyclase. In a study which was performed on 7 patients with HPS and advanced liver cirrhosis, it had several effects: increase of PO_2, decrease of $\Delta P(A-$

a)O_2, decrease of shunt fraction and increase of mean pulmonary artery pressure, increase of pulmonary vascular resistance and lowered cardiac output. Beneficial effects on gas exchanged continued up to 10 hours. Methylene blue is potentially effective for treatment of HPS although transiently. It might be used in the post-OP period of liver transplantation in cases who have transient hypoxemia, however its routine and long term use is not recommended due to lack of adequate data regarding side effects in long term periods, beneficial effects of No in body defense and bluish discoloration of mucous membranes and secretions[57].

Interventions other than liver transplantation:

Embolotherapy: It is recommended that pulmonary angiography be done for those HPS patients who respond poorly to breathing 100% oxygen i.e., PaO_2<150-200mmHg. If coil type II vascular lesions are diagnosed, embolotherapy with 22-coil spring devices must be tried first, since it is seen that this group of HPS patients responds poorly to liver transplantation due to responsible A-V communications which are less amenable to closure after liver transplantation.

Portal decompression wtih transjugular intrahepatic portosystemic shunt (TIPS): Regarding probable role of portal hypertension in the pathogenesis of HPS, portal decompression is suggested as a potential way for improving HPS.

There is controversy regarding above mentioned beneficial effects of the above mentioned technique on HPS. Some studies confirmed and HPS others ruled out usefulness of TIPS. Overall, TIPS could be considered as a palliative treatment and/or as a bridge to orthotopic liver transplantation in severe hypoxemic HPS patients since liver transplantation may be dangerous in profound hypoxemia. More researches are needed undoubtfully.

In a retrospective analysis in 22 patients with HPS, the mortality rate was approximately 41% after a mean follow-up of 2.5 years[12.] A prospective study on the prognostic significance of HPS showed that HPS is an independent predictor of survival, and mortality correlates with HPS severity. As the presence of HPS independently worsens the prognosis of cirrhotic patients, its presence should influence clinical management.

If patients are on the waiting list for liver transplantation, the presence of HPS should be combined with the MELD (model for end-stage liver disease) score to accelerate the process for liver transplantation.

A retrospective study by Krowka et al[39] reported an improvement or normalization of hypoxemia in about 80% of patients after liver transplantation. A prospective study by Battaglia et al [42]also demonstrated resolution of intrapulmonary

shunting in patients with HPS after liver transplantation. It is thus considered that HPS may be reversed after liver transplantation. The pulmonary vascular changes after successful transplantation show a slow remodeling process that may take a long time for symptom relief. It has been found that the lower the preoperative PaO2, the longer the time to decrease the alveolar-arterial pressure gradient and to improve arterial oxygenation.

However, retrospective data show that there is a higher mortality rate after liver transplantation in patients with HPS than in those without HPS. Unique postoperative complications in patients with HPS have been described, which include pulmonary hypertension[45,46], embolic cerebral hemorrhage[47] and postoperative deterioration in oxygenation. These unique postoperative complications, along with delayed resolution of hypoxemia, are implicated in the higher mortality rate. For patients with severe preoperative hypoxemia (PaO2 $\leq$50 mmHg) and significant intrapulmonary shunting (Tc-99m MAA shunt fraction $\geq$20%), the mortality rate may increase further after liver transplantation[39, 48].

AIMS AND OBJECTIVES

1) To evaluate the Prevalence and clinical profile of hepatopulmonary syndrome in a tertiary care hospital

2) To study the clinical spectrum of HPS in cirrhotic patients

3) To correlate severity of HPS with child Pugh score.

MATERIALS AND METHODS

Setting: Department of medicine, medicalgastroenterology Government Rajaji hospital and Madurai medical college, Madurai.

Design of study: Prospective analytical study.

Period of study: November 2006 to April 2007

Ethical committee approval: The present project was approved by the ethical committee.

Criteria for selection of subjects:

Rigid criteria were adopted for inclusion and exclusion of cases and controls for the present study. The details are furnished below.

Inclusion criteria:

1. All the cirrhosis patients confirmed by clinical, biochemical, ultrasound imaging. Liver biopsy was not done

Exclusion criteria:

1. Patients with known cardiovascular and respitatory diseases
2. Other co morbid conditions which could explain hypoxemia
3. Those with hepatic encephalopathy, bedridden patients, patients with active uncontrolled upper gastrointestinal hemorrhage
4. Active smokers
5. Patients having intra cardiac shunts in echocardiography
6. Patients who were not willing to participate in the study.
7. Children below 12 years.

Consent:

Informed consent was obtained from all those who participated in the study.

Materials:

Thus a total of 73 cases that satisfied the inclusion and exclusion criteria stated above were taken up for the study.

Methods:

Selected sociodemographic, clinical and laboratory data were collected from the both inpatients and out patients of department of medicine and medicalgastroenterology and recorded in a pro forma.

Socio demographic data comprised of:

- age
- sex
- locality
- occupation

Clinical data comprised of:

- Dyspnea
- Platypnoea
- H/o Alcoholism, drugs
- Cyanosis
- Clubbing
- Jaundice
- Ascites
- systemic examination

Laboratory data included:

- Hb ,TC,DC
- Urine - albumin, deposits, Sugar
- Blood Sugar
- Urea
- Creatinine
- Liver function tests
- Prothrombin time
- Viral markers – HbsAg, AntiHCVAb
- Electrolytes
- ARTERIAL BLOOD GAS ANALYSIS
- ECG, CHEST X RAY
- **Imaging studies**
- OGD
- USG ABDOMEN
- Contrast enhanced echocardiography(CEE)

CEE procedure (using Aloka SSD 4000) was carried out in all patients to detect the presence of IPVD. A three way cannula and intra cath was fixed to the antecubital vein of the right forearm. Initial M-mode and 2-D echocardiography and colour Doppler study were carried out to exclude the presence of intracardiac shunts. Micro agitated saline was prepared in the injecting syringe and 10ml was

injected rapidly into the veins of the right forearm. Both right and left heart chambers were visualized on 2-D echocardiography to look for the appearance of the contrast. The study was repeated at the same sitting with M-mode echocardiography. The timing of appearance of the contrast in the left heart chambers following it's appearance in the right heart chambers, in terms of heart beats, was documented. Appearance of the contrast in the left heart chambers 3-6 beats after it's appearance on the right side was taken as evidence of intrapulmonary shunting.

ABG test was performed (using SIEMENS ANALYZER) in patients vertical position, the oxygenation saturation, arterial blood oxygen, (A-a) O2 gradient and were evaluated.

Definitions

Child's classification was done according to Child –Turcotte-Pugh score

Parameter	Numerical score		
	1	2	3
Ascites	None	Slight	Moderate
Encephalopathy	None	Slight /moderate	Moderate/severe
Bilirubin (mg/dl)	<2	2 – 3	>3
Albumin (g/dl)	>3.5	2.8 – 3.5	<2.8
Prothrombintime(Seconds increased)	1 - 3	4 – 6	>6

Total numerical score	Child- Turcotte-Pugh score
5 – 6	A
7 – 9	B
10 – 15	C

Criteria for Alcoholic liver disease

Defined as intake of 40 – 80 gm of alcohol per day for minimum of 10 years

Clinical HPS

Clinical HPS was diagnosed in a patient with positive CEE and Po2 below 80mmHg.

Subclinical HPS

Positive CEE and Po2 between 80mmHg -90mmHg were taken as sub clinical HPS.

IPVDS

Positive CEE and Po2 >90 mmHg were taken as Intrapulmonary vascular dilatation syndrome (IPVDS).

Conflict of interest:

There was no conflict of interest.

support:

Nil.

Statistical analysis:

Data were entered in Microsoft Excel spread sheet and analyzed utilizing the software - epidemiological information package 2002 (Epi Info 2002)- developed by centre for disease control and prevention, Alaska for World Health Organization. Range, mean, standard deviation and 'p' values were calculated using this package. Significance was considered if the 'p' value was below 0.05.

OBSERVATIONS AND RESULTS

Table 1

Age composition

Age Group in years	Total no Cases	
	No.	%
< 30	3	4.1
31-40	12	16.4
41-50	18	24.7
51-60	20	27.4
61-70	14	19.2
> 70	6	8.2
Total	73	100
Mean	52.2 yrs	
S.D.	13.0 yrs	

Total of 73 patients were studied .age of cases ranges from 24years to 78 years

Mean age was 52.2 ± 13 years

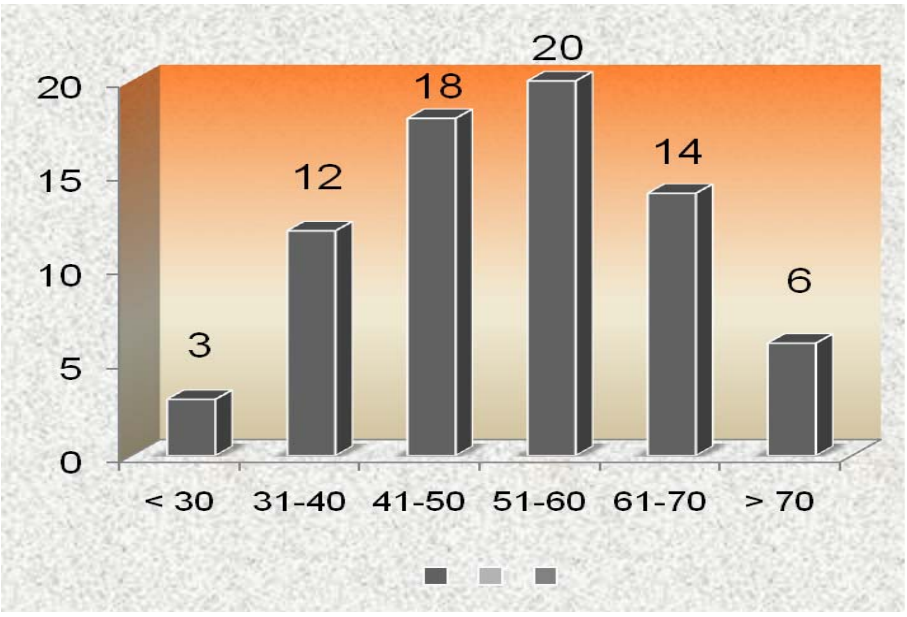


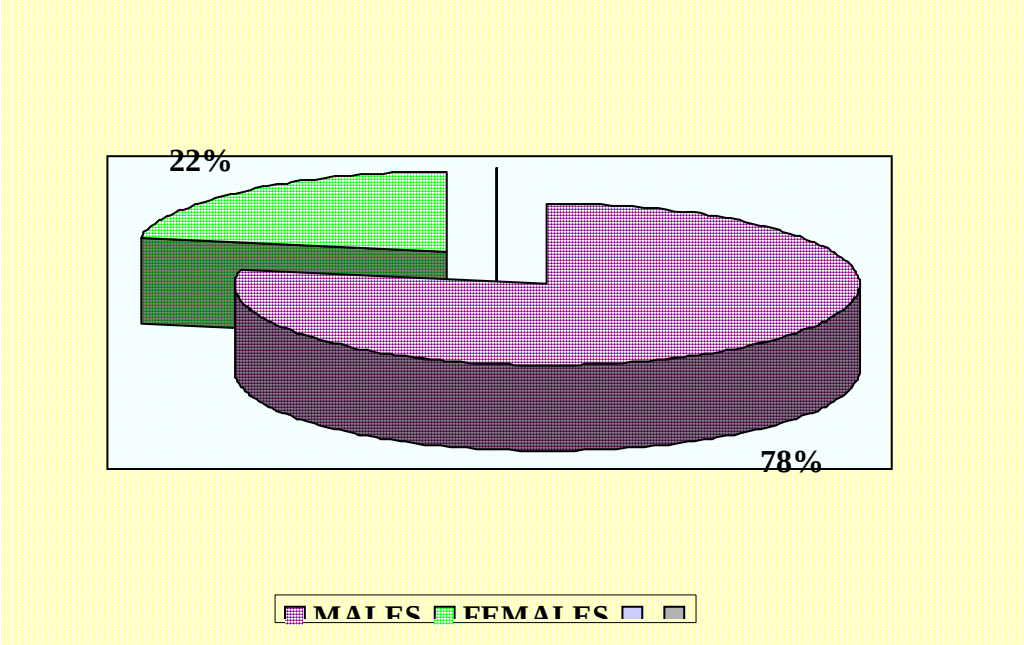
Table 2

Sex composition

Sex	Cases	
	No.	%
Males	57	78.1
Females	16	21.9
Total	73	100

Among 73 cases studied there were 57 males and 16 females

Sex composition



Aetiology of cirrhosis

Among 73 cirrhotic 34 were alcoholics, HBs antigen was present in 6 patients, and Anti HCV antibody was present in 6 patients, In other 27 patients aetiology was not known.

The tables were given below.

Table 3

Alcoholism

Alcoholism	Cases	
	No.	%
Yes	34	46.6
No	39	53.4
Total	73	100

Alcoholism

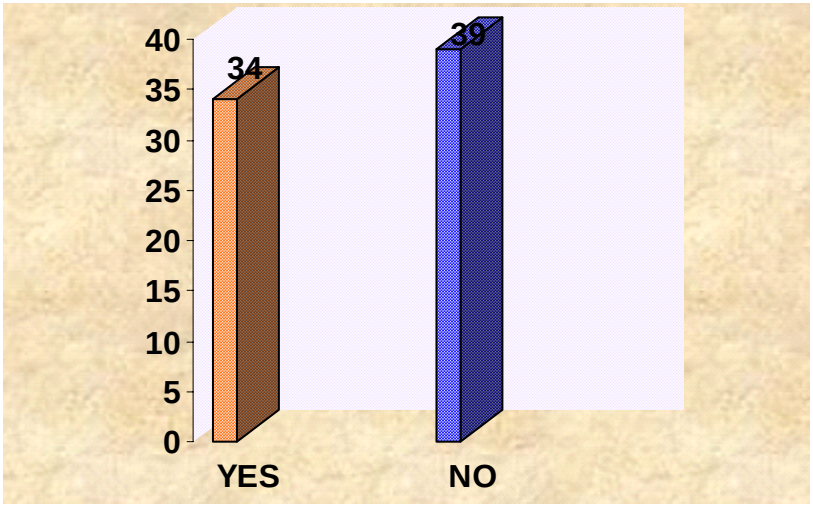


Table 4

HBsAntigen

HBs Antigen	Cases	
	No.	%
Present	6	8.2
Absent	67	91.8

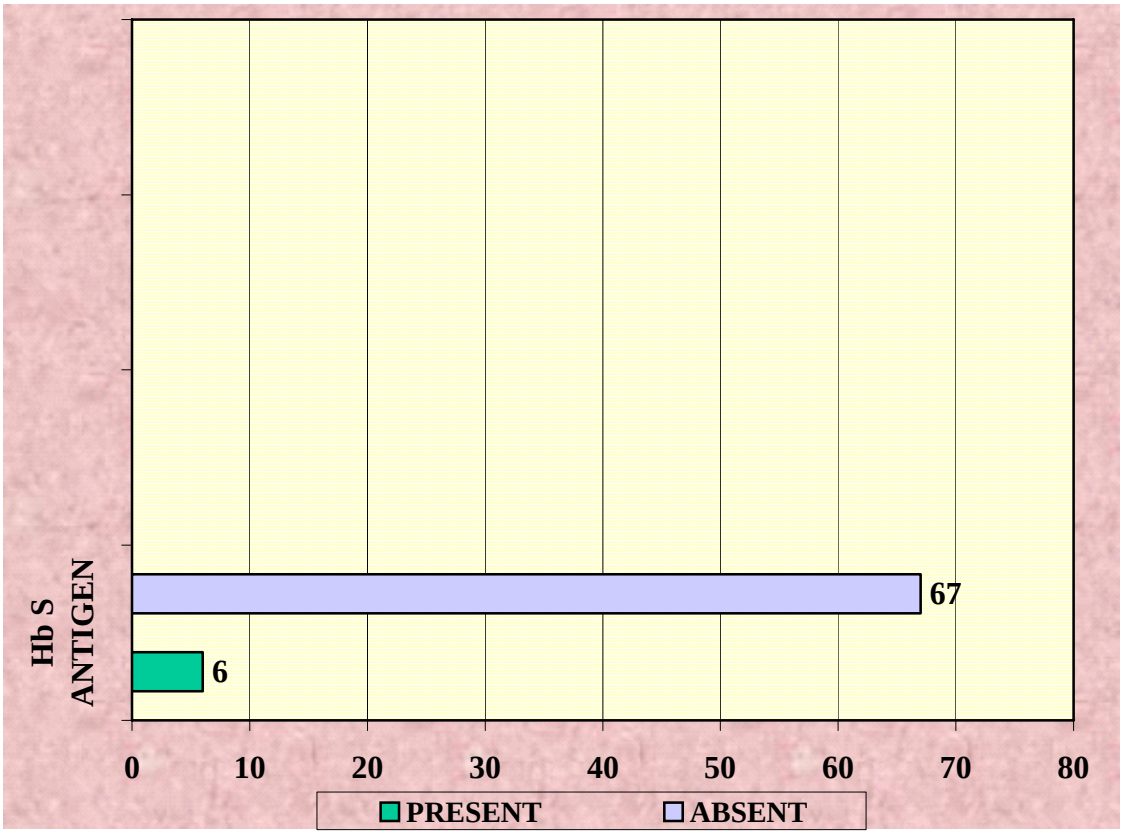


Table5

AntiHCVAntibody

Anti HCV Antibody	Cases	
	No.	%
Present	6	8.2
Absent	67	91.8

Anti HCV Antibody

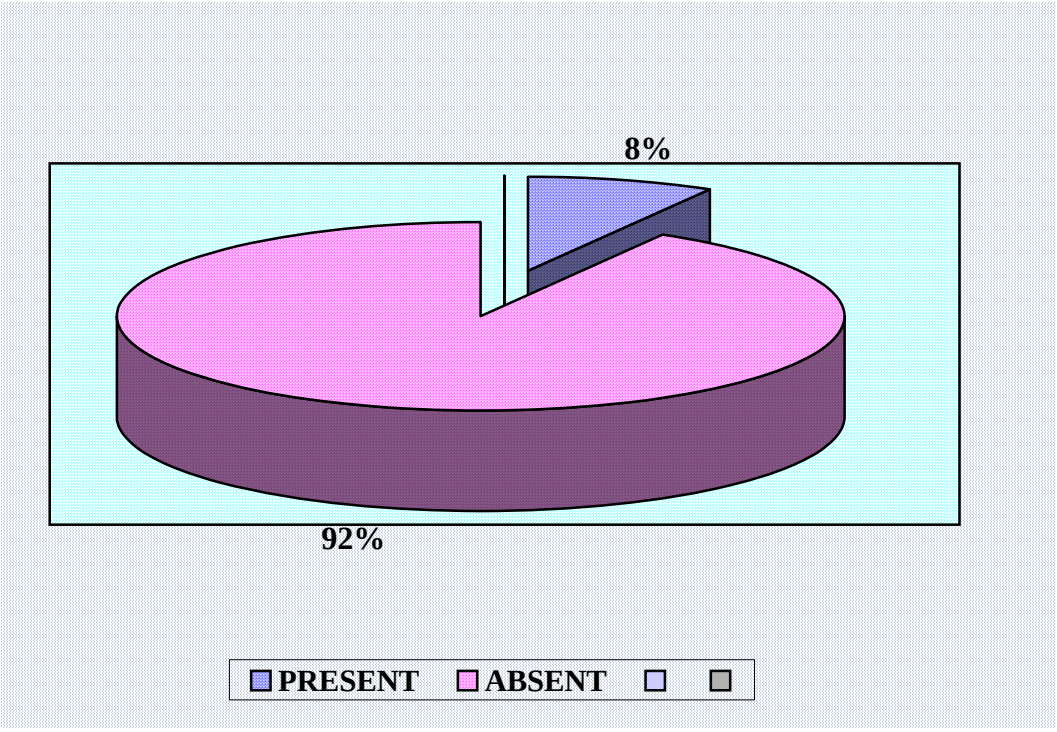


Table 6

Clinical features

Clinical features	HPS(N=9)		SUB HPS(N=6)		IPVDS(N=17)		p
	No.	%	No	%	No	%	
Dyspnea	8	88.9	0	0	8	47.0	0.001
Platypnea	2	22.2	0	0	0	0	0.07
Cyanosis	9	100	0	0	0	0	0.0024
Clubbing	7	77.8	2	33.3	3	17.6	0.009
Spider naevi	2	22.2	0	0	0	0	0.04

Commonest symptom was dyspnea which occurs in 88.9 % of patients with HPS, 47% of patients with IPVDS. Platypnea was present in 2 patients of HPS and was not present in subclinical HPS or IPVDS patients.

All the patients of HPS had cyanosis. Clubbing was seen in 77.8% of HPS, 33.3% of subclinical HPS, 17.6% of IPVDS patients respectively.

Dyspnea, cyanosis, clubbing, Spider naevi were significantly higher in HPS than other two groups.

Table 7

Child's classification

Child's Classification	Cases	
	No.	%
A	25	34.2
B	37	50.7
C	11	15.1
Total	73	100

Among 73 patients 25(34.2%) were in child A, 37(50.7%) were in child B, 11(15.1%) were in child C.

CHILD'S CLASSIFICATION

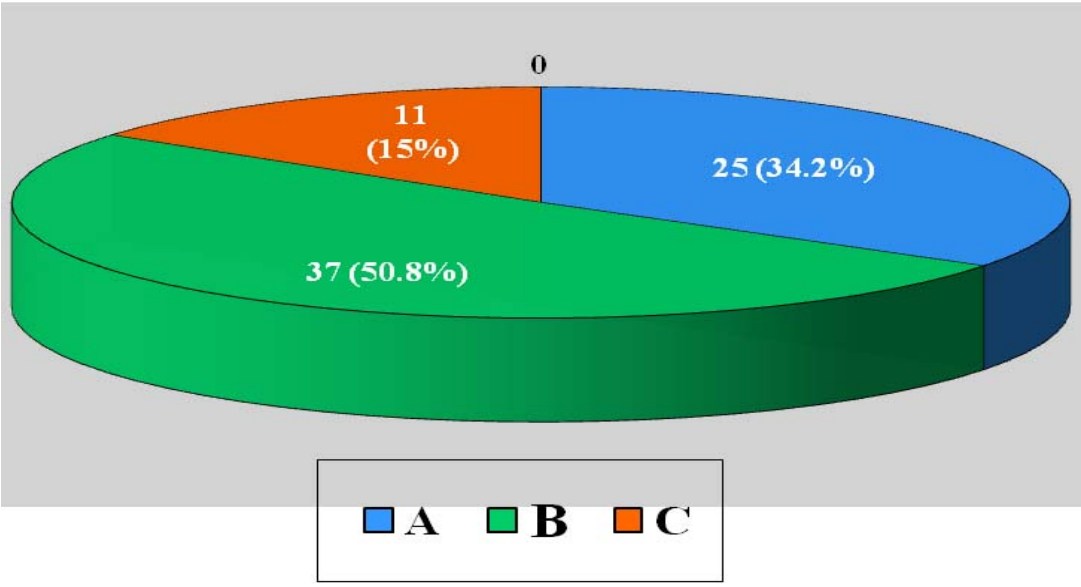


Table 8

Contrast echo

Contrast Echo	Cases	
	No.	%
Positive	32	43.8
Negative	41	56.2
Total	73	100

Contrast echo was positive in 32 patients (43.8%) and was negative in 41 patients (56.2%)

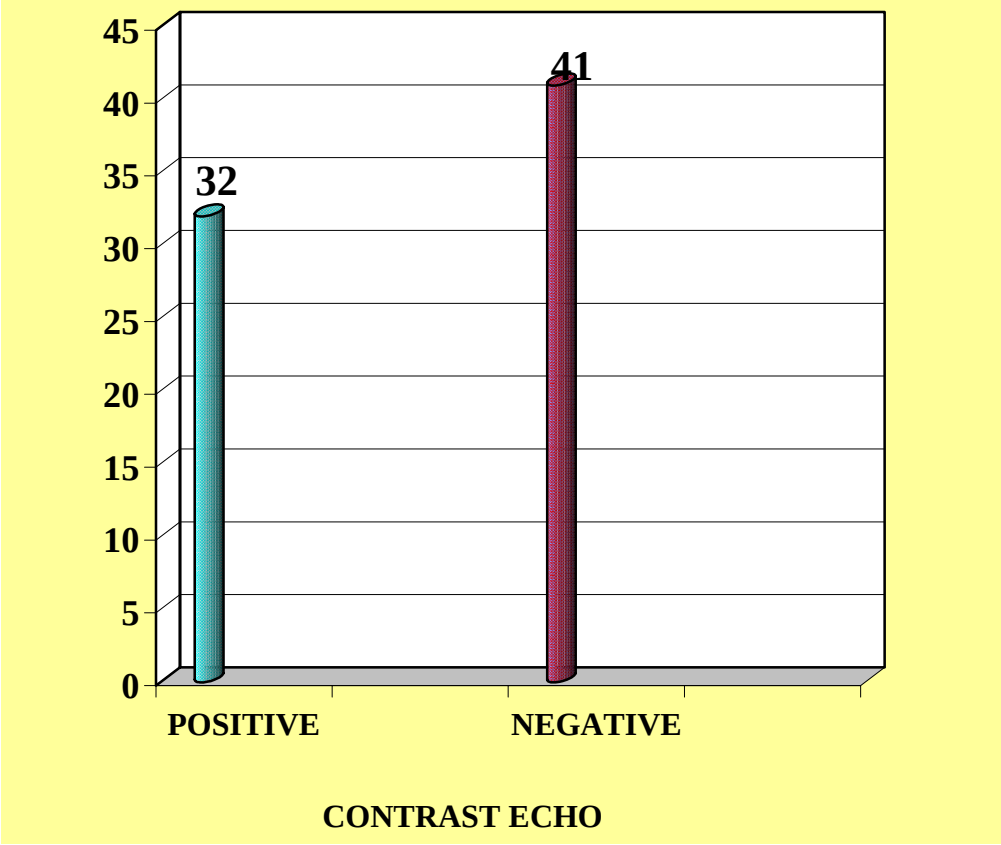


Table 9

Relationship between child's classification and contrast echo

Child's Classification	Contrast Echo			
	Positive		Negative	
	No.	%	No.	%
A (25)	6	24	19	76
B (37)	19	51.4	18	48.6
C (11)	7	63.6	4	36.4
'p'	0.0666 (not Significant)			

There was no significant correlation between positive CEE and child's classification

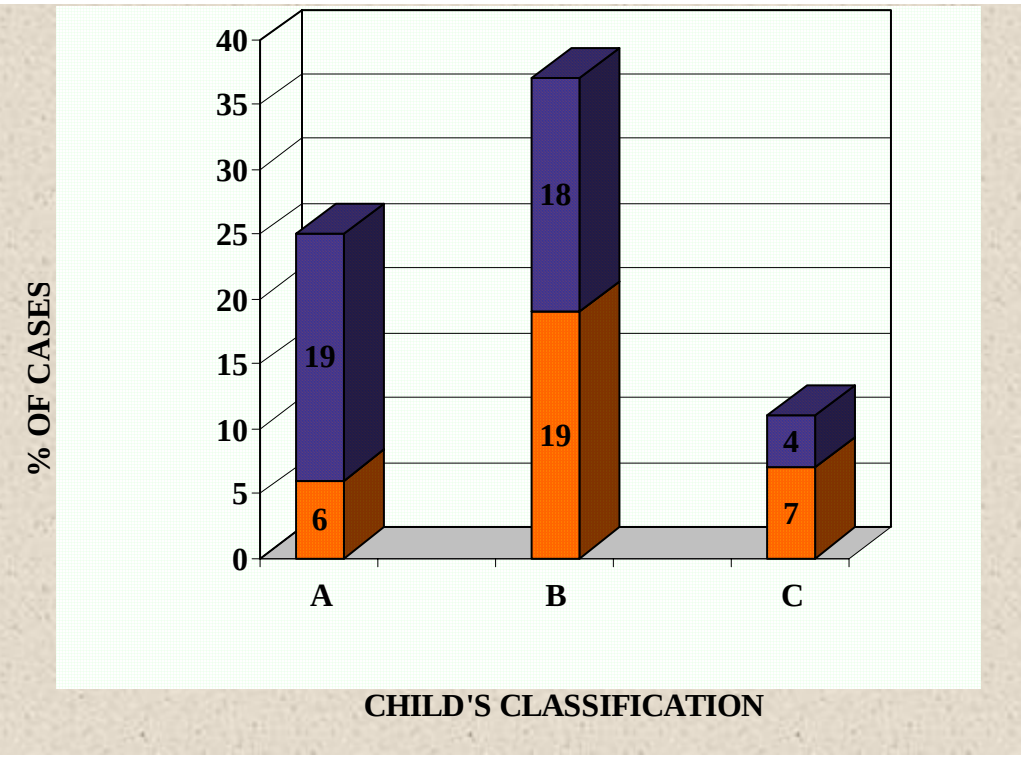


Table 10

Relationship between Child's classification, PaO_2 and Contrast Echo

Child's classification and PaO_2	Contrast Echo			
	Positive		Negative	
	No.	%	No.	%
A (25)				
PaO_2 < 80	1	4	3	12
PaO_2 80-90	-	-	3	12
PaO_2 >90	5	20	13	52
Total	6	24	19	76
B (37)				
PaO_2 < 80	3	8.1	5	13.5
PaO_2 80-90	5	13.5	4	10.8
PaO_2 >90	11	29.7	9	24.3
Total	19	51.3	18	48.7
C (11)				
PaO_2 < 80	5	45.5	1	9.1
PaO_2 80-90	1	9.1	1	9.1
PaO_2 >90	1	9.1	2	18.1
Total	7	63.7	4	36.3

In child A out of 25 patients 6 had positive CEE in which one had pao2 < 80mmHg and 5 had pao2 > 90 mmHg.

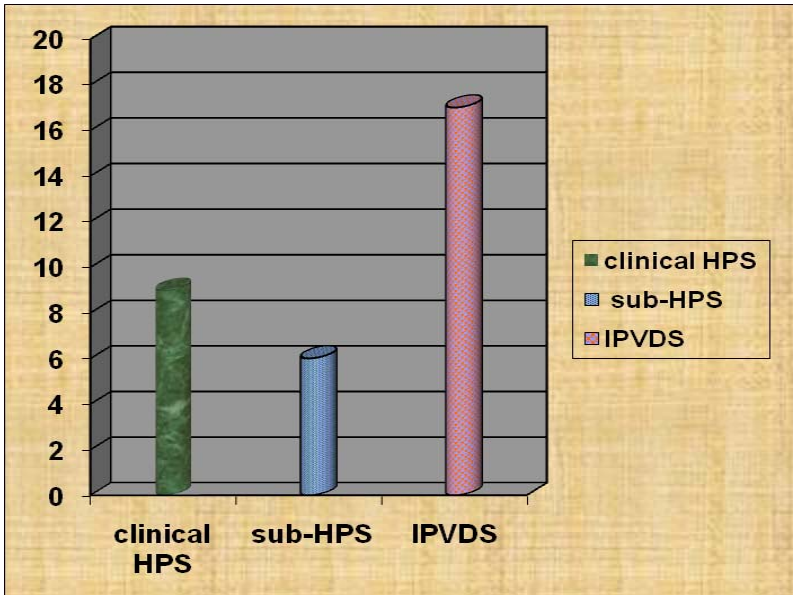
In child B out of 37 patients 19 had positive CEE in which 3 had pao2 <80, 5 had pao2 between 80-90, 11 had pao2 > 90 mmHg

In child C out of 11 patients 7 had positive CEE in which 5 had pao2 <80, I had pao2 between 80-90, and I had pao2 > 90 mmHg.

Table 11

Prevalence of HPS

CLINICAL SPECTRUM	No OF PATIENTS	% N=73
CLINICAL HPS	9	12.3
SUBCLINICAL HPS	6	8.2
IPVDS	17	23.3



Among 73 patients 9 (12.3%) had clinical HPS, 6 (8.2%) had sub clinical HPS, 17 (23.3%) had IPVDS.

Table 12

Relationship between HPS and age

Clinical spectrum	Age in years	
	Mean	S.D.
Clinical HPS (9)	53.89	14.13
Sub clinical HPS (6)	47.33	7.94
IPVDS (17)	53.47	11.71
'p'	0.4594 (Not significant)	

There is no significant relationship between HPS and age

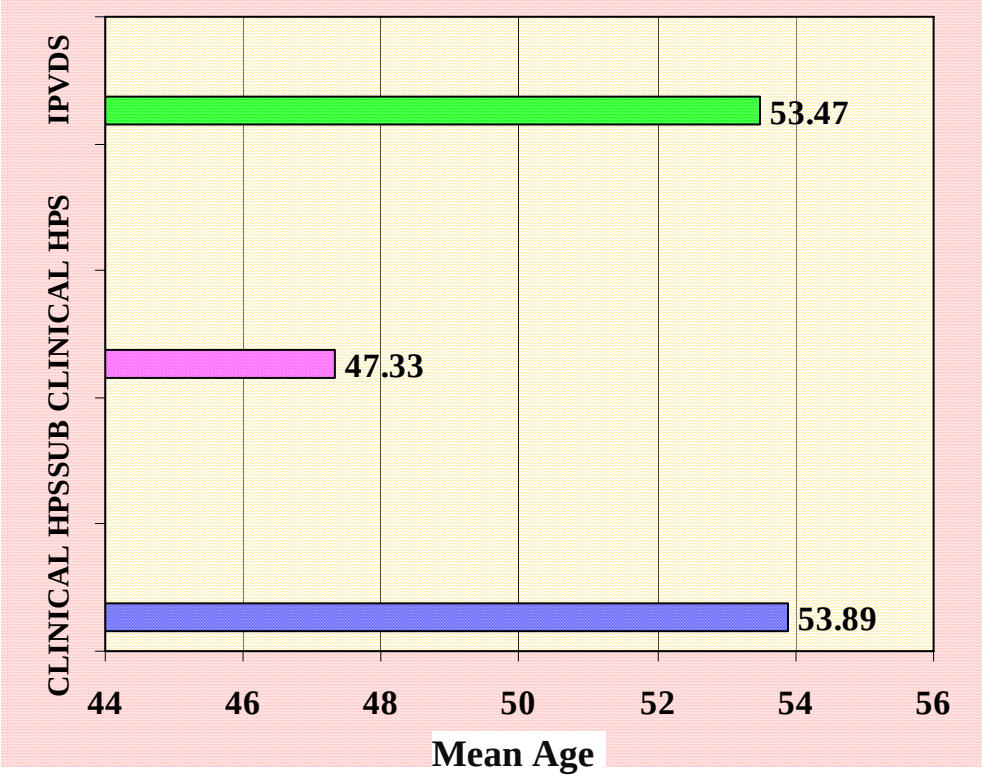


Table 13

Relationship between HPS and gender

Clinical spectrum	Sex			
	Males		Females	
	No.	%	No.	%
Clinical HPS (9)	8	88.9	1	11.1
Sub clinical HPS (6)	5	83.3	1	16.7
IPVDS (17)	11	64.7	6	35.3
P	0.0723 not significant			

There is no significant relationship between HPS and gender

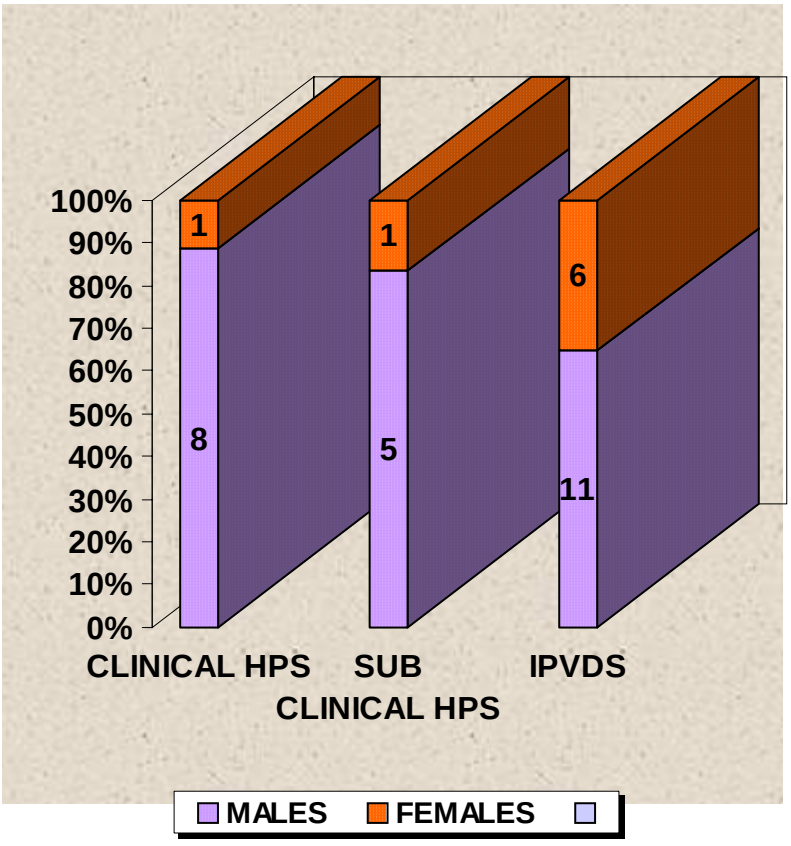


Table 14

RELATIONSHIP BETWEEN HPS AND CHILD'S CLASSIFICATION

Clinical Spectrum	Child's A	Child's B	Child's C
Clinical HPS (9)	1(11.1%)	3(33.3%)	5(55.6%)
SubclinicalHPS (6)	0	5(83.3%)	1(16.7%)
IPVDS (17)	5(29.4%)	11(64.7%)	1(5.9%)
	P 0.0626 not significant		

In child A Prevalence of HPS, subclinical HPS, IPVDS were 11.1%, 0, and 29.4% respectively. In child B Prevalence of HPS, subclinical HPS, IPVDS were 33.3%, 83.3%, 64.7% respectively. In child C Prevalence of HPS, subclinical HPS, IPVDS were 55.6%, 16.7%, 5.9% respectively.

There is no significant correlation between child's classification and occurrence of HPS

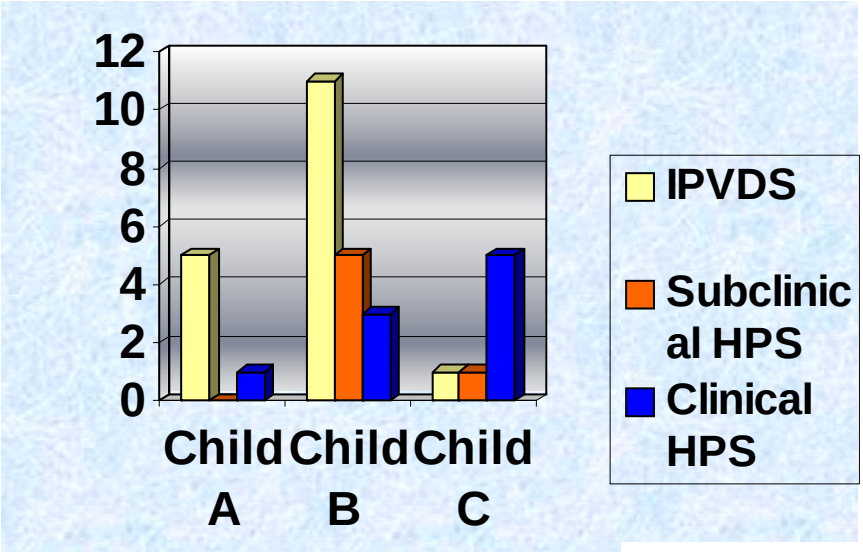
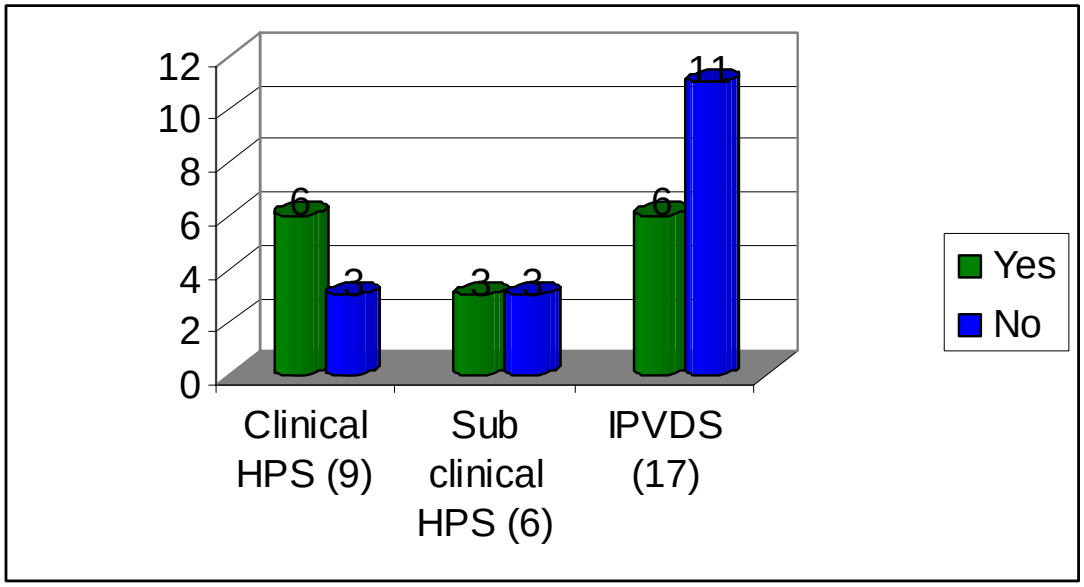


Table 15

RELATIONSHIP BETWEEN HPS AND Alcoholism

Clinical spectrum	Alcoholism			
	Yes		No	
	No.	%	No.	%
Clinical HPS (9)	6	66.7	3	33.3
Sub clinical HPS (6)	3	50	3	50
IPVDS (17)	6	35.3	11	64.7

P 0.0721 (not significant)



Six cases of clinical HPS, three cases of subclinical HPS, six cases of IPVDS were occurring in alcoholics.

Table 16

Relationship between HPS and HBsAg

Clinical spectrum	Hb S Antigen			
	Present		Absent	
	No.	%	No.	%
Clinical HPS (9)	2	22.2	7	77.8
Sub clinical HPS (6)	2	33.3	4	66.7
IPVDS (17)	1	5.9	16	94.1

P 0.1030 not significant

HBsAg was positive in two cases of clinical HPS, two cases of subclinical HPS and one case of IPVDS.

Table 17

Relationship between HPS and HCV

Clinical spectrum	Anti HCV Antibody			
	Present		Absent	
	No.	%	No.	%
Clinical HPS (9)	-	-	9	100
Sub clinical HPS (6)	1	16.7	5	83.3
IPVDS (17)	3	17.6	14	82.4

p 0.1376 not significant

AntiHCV Antibody was present in three cases of IPVDS, one case of subclinical HPS, and none of clinical HPS patients.

Aetiology of cirrhosis had no significant correlation with HPS

DISCUSSION

Hepatopulmonary syndrome includes the triad of liver disease, arterial blood deoxygenation and intra pulmonary pulmonary shunts.

Among 73 cases studied the mean age of patient was 52.2 ± 13 years with a range of 24 to 78 years.

Regarding sex distribution male female ratio was 3: 1.since alcoholic liver disease is most common cause of cirrhosis in our country, alcoholism is more prevalent in males. This explains higher incidence of cirrhosis in males.

Dyspnea

In our study among 73 patients 31 (42.46%) had symptom of dyspnea, 16 (51.6%) of those showed evidence of intrapulmonary shunt. H.S Hira et al (2003) found that 60% had symptom of dyspnea and (55.5%) showed evidence of shunt [48]. Dyspnea was present in 88.9% of clinical HPS patients, 47% of IPVDS patients and none of subclinical HPS patients. P schenk et al (2002) stated that dyspnea was present in 57% of compared with 8% of subclinical HPS and 6% of patients without HPS[51]. Sarin et al (2006) showed dyspnea was present in 84.6% of HPS patients[54]. In our study platypnea was occur in 2 of 9 (22.2%) HPS patients. This suggested that dyspnea was a reasonably sensitive but poorly specific clinical indicator of

intrapulmonary shunt. In the absence of any cardiopulmonary disease this symptom could suggest a pulmonary vascular complication of liver disease.

Cyanosis

In our study all the 9 patients of HPS and none among remaining 64 cases were found to have cyanosis showing 100% sensitivity and specificity.

This is parallel with the observation made by H.S Hira et al (2003)[48]. It is likely that observation was an exaggeration of the true usefulness of this marker and could have resulted from the strict exclusion criteria for cardiopulmonary diseases.

Clubbing

In our study Clubbing was present in 7 of 9 (77.8%) of clinical HPS, 1 (33.3%) patient of subclinical IPVDS patients. Only 2 among remaining 41 patients showed clubbing. If we take HPS alone, presence of clubbing showed sensitivity of 77.8% and specificity of 92%. Hira et al(2003) had found that presence of clubbing showed sensitivity and specificity of 100% and 96% respectively[48]. In sarin et al (2006) clubbing was present in 92.3% 0f HPS patients[54]. In our study spider naevi was present in 2 of 9 (22.2%) HPS patients and was not present in remaining patients. In sarin et al (2006) spider naevi was present in 61.5% of HPS patients[54].

Contrast echo

In our study Contrast echo was positive in 32 of 73 (43.8%) patients. In Hira et al(2003) positive CEE was 33.34%, in sarin et al(2006) it was 30.3% , P schenk et al(2002) it was 34%, mimidis KP(1998) et al it was 10.7%[52], Anand AC et al(2001) it was 27%[50], Binay K de et al(2000) it was 8.9%[49].The reason for higher number of positive contrast echo in present study may be that majority of patients 31 0f 73 selected were presented with dyspnea and patients associated with cardiopulmonary disease leading to hypoxemia were excluded. There is no significant correlation between child's classification and positive contrast echocardiography.

Hypoxemia

Hypoxemia caused by intrapulmonary shunting in sitting position was found in 15 (20.5%) patients. Hypoxemia without shunt in sitting position was found in17 (23.3%). Hypoxemia without shunt was higher than in with shunt. This is parallel with the observation made by culafic Dj et al(2000)[53] .Hypoxemia is common in patients with chronic liver disease. A rare cause is HPS. Because other abnormalities (eg ascites) or minor shunts that couldn't be detected by contrast echo may coexist in cirrhotic patients and contribute to respiratory insufficiency. Measurement of lowered PO_2 alone is not sufficient to make diagnosis of HPS

Prevalence of HPS

In our study prevalence of HPS was 12.2%, subclinical HPS was 8.2%, IPVDS was 23.2%.sarin et al (2006) had found that prevalence of HPS, subclinical HPS and IPVDS were 9.8%, 20.5%, 30.3% respectively. In Hira et al (2003) prevalence of HPS was 16.67%. Amir Houshang mohammad Alizadeh et al (2006) had found that prevalence of HPS and IPVDS were 18.5%, 13% respectively[56].In Anand AC et al (2001) prevalence of HPS was 17.5% and IPVD was 27%[50]. In Binay K de et al (2000) prevalence of HPS was 8.9%.

There is no significant relationship between HPS and age, sex, aetiology

Regarding aetiology in our syudy most common aetiology was alcohol, but Amir Houshang Alizadeh et al(2006) had found that most common aetiology was HBV, but there was no significant relation[56]. In Anand AC et al(2001) Age, sex, duration of symptoms were not different in patients with HPS[50].

Correlation between HPS and child's classification was controversial. In our study among 9 cases of clinical HPS, Five occur in child C, Three in child B, One in child A, though child score was higher in clinical HPS group but did not reach statistical significance. This observation was consistent with earlier reports. Same results were observed in sarin et al(2006)[54]. Hira et al(2003) showed that child's

grading of liver disease did not influence the incidence of HPS and IPVDS[48]. Binay k de et al (2000) showed that there was no clear relationship with severity of cirrhosis by child's grading[49]. In P schenk et al (2002) child's grading correlated significantly with severity of HPS. Interestingly studies conducted by sood N et al (2001) observed that 50 patients were studied for intrapulmonary shunt but none had evidence of IPVD. IPVD was not observed in their study[55].

Failure to recognize HPS can be serious because progressive decline in oxygenation can occur despite stable liver function at a mean 2.5 years after onset of dyspnea,41% mortality has been reported . Another reason to recognize HPS early is that it is treatable. The treatment of choice for cirrhotic patients, however is orthotopic liver transoplantation , but this is often complicated by intractable post operative hypoxemia. Current evidence indicates that a successful outcome is possible in the presence of post operative hypoxemia, but morbidity and mortality remain high.

Our study emphasizes that early detection of HPS in cirrhotic patients helps in reduction in morbidity and mortality and thereby increasing prognosis.

CONCLUSION

- HPS is well known but often under recognized common complication in cirrhosis
- Dyspnea was commonest symptom in HPS patients. HPS should be suspected in a cirrhotic who complaining of dyspnea and particularly Platypnea.
- Cyanosis was a strong predictive marker of HPS if strict exclusion criteria for cardiopulmonary diseases were followed.
- Contrast enhanced echo and ABG were an easy and cheap method of identifying shunts in pulmonary circuit.
- Age, Sex, Aetiology of cirrhosis had no influence on presence of HPS
- There was no correlation between child's classification and HPS

SUMMARY

Hepatopulmonary syndrome includes the triad of liver disease, arterial blood deoxygenation and intra pulmonary pulmonary shunts. This study was conducted to evaluate the Prevalence and clinical profile of hepatopulmonary syndrome and to study the clinical spectrum of HPS in cirrhotic patients .

After institutional ethical clearance, with an informed consent and with rigid criteria, 73 patients were selected carefully and were evaluated on social, clinical and laboratory aspects. The data were entered in Micro soft Excel spread sheet and analyzed statistically.

There were 57 males and 16 females; Mean age was 52.2 ± 13 years. Among 73 patients 25 were in child A, 37were in child B, 11were in child C. Commonest symptom was dyspnea which occurs in 88.9 % of patients with HPS, 47% of patients with IPVDS. Dyspnea was a reasonably sensitive but poorly specific clinical indicator of intrapulmonary shunt. In the absence of any cardiopulmonary disease this symptom could suggest a pulmonary vascular complication of liver disease

All the patients of HPS had cyanosis. Cyanosis was a strong predictive marker of HPS if strict exclusion criteria for cardiopulmonary diseases were followed.

Dyspnea, cyanosis, clubbing, Spider naevi were significantly higher in HPS than other two groups.

Hypoxemia is common in patients with chronic liver disease. A rare cause is HPS. Because other abnormalities (eg ascites) or minor shunts that couldn't be detected by contrast echo may coexist in cirrhotic patients and contribute to respiratory insufficiency. Measurement of lowered PO2 alone is not sufficient to make diagnosis of HPS.

In our study prevalence of HPS was 12.2%, subclinical HPS was 8.2%, and IPVDS was 23.2%

There is no significant relationship between HPS and age, sex, aetiology. Regarding aetiology in our study most common aetiology was alcohol. Though child score was higher in clinical HPS group but did not reach statistical significance.

POSTIVE CONTRAST ENHANCED ECHO CARDIOGRAPHY

NEGATIVE CONTRAST ENHANCED ECHO CARDIOGRAPHY

BIBLIOGRAPHY

1. Fluckiger M. Vorkommen von trommelschlägelförmigen fingerendphalangen ohne chronische veränderungen an derlungen oder am herzen. *Wien Med Wschr* 1884;34:1457.
2. Kennedy TC, Knudson RJ. Exercise-aggravated hypoxemia and orthodeoxia in cirrhosis. *Chest* 1997;72:305–9.
3. Krowka MJ. Hepatopulmonary syndrome versus portopulmonary hypertension: distinctions and dilemmas. *Hepatology*1997;25:1282–4.
4. PA, Stoller JK. The hepatopulmonary syndrome. *AnnIntern Med* 1995;122:521–9.
5. Castro M, Krowka MJ. Hepatopulmonary syndrome. A pulmonary vascular complication of liver disease. *Clin Chest Med*1996;17:35–48.
6. Krowka MJ, Tajik AJ, Dickson ER, Wiesner RH, Cortese DA.Intrapulmonary vascular dilatations (IPVD) in liver transplantcandidates. Screening by two-dimensional contrast-enhanced echocardiography. *Chest* 1990; 97:1165–70.
7. Stoller J, Lange P, Westveer M, Carey W, Vogt D, Henderson M. Prevalence and reversibility of the hepatopulmonary syndrome after liver

transplantation—the Cleveland Clinic experience. *West J Med* 1995; 163:133–8.

8. Abrams GA, Jaffe CC, Hoffer PB, Binder HJ, Fallon MB. Diagnostic utility of contrast echocardiography and lung perfusion scan in patients with hepatopulmonary syndrome.*Gastroenterology* 1995;109:1283–8.

9. Rodrigues-Roisin R, Roca J, Augusti A, Mastai R, Wagner P, Bosch J. Gas exchange and pulmonary vascular reactivity in patients with liver cirrhosis. *Am Rev Respir Dis* 1987;135:1085–92.

10. Vachiery F, Moreau R, Hadengue A, Gadano A, Soupison T,Valla D, Lebrec D. Hypoxemia in patients with cirrhosis: relationship with liver failure and hemodynamic alternations.*J Hepatol* 1997;27:492–5.

11. Abrams GA, Nanda NC, Dubovsky EV, Krowka MJ, Fallon MB. Use of macroaggregated albumin lung perfusion scan to diagnose hepatopulmonary syndrome: a new approach.*Gastroenterology* 1998;114:305–10.

12. Krowka MJ, Dickson ER, Cortese DA. Hepatopulmonary syndrome: clinical observations and lack of therapeutic response to somatostatin analogue. *Chest* 1993;104:515–21.

13. Fallon MB, Abrams GA, McGrath JW, Hou Z, Luo B. Common bile duct ligation in the rat: a model of intrapulmonary vasodilatation and hepatopulmonary syndrome. *Am J Physiol*1997;272:779–84.

14. Fallon MB, Abrams GA, Luo B, Hou Z, Dai J, Ku DD. The role of endothelial nitric oxide synthase in the pathogenesis of a rat model of hepatopulmonary syndrome. *Gastroenterology* 1997; 113:606–14.

15. Luo B, Abrams G, Fallon MB. Endothelin-1 in the rat bile duct ligation model of hepatopulmonary syndrome: correlation with pulmonary dysfunction. *J Hepatol* 1998;29:571–8.

16. Luo B, Liu L, Tang L, Zhang J, Stockard C, Grizzle W, FallonMB. Increased pulmonary vasculature endothelin B receptor expression and responsiveness to endothelin-1 in cirrhotic and portal hypertensive rats: a potential mechanism in experimental hepatopulmonary syndrome. *J Hepatol* 2003;38:556–63.

17. Cremona G, Higenbottam TW, Mayoral V, Alexander G,Demoncheaux E, Borland C, Roe P, et al. Elevated exhaled nitric oxide in patients with hepatopulmonary syndrome. *Eur Respir J* 1995;8:1883–5.

18. Nunes H, Lebrec D, Mazmanian M, Capron F, Heller J, Tazi KA, Zerbib E, et al. Role of nitric oxide in hepatopulmonarysyndrome in cirrhotic rats. *Am J Respir Crit Care Med* 2001;164:879–85.

19. Levias A, Jimenez W, Lamas S, Bosch-marce M, Oriola J, ClariaJ, Arroyo V, et al. Endothelin 1 does not play a major role in the homeostasis of arterial pressure in cirrhotic rats with ascites. *Gastroenterology* 1995;108:1842–8.

20. Tsai YT, Lin HC, Yang MCM, Lee FY, Hou MC, Chen LS, LeeSD. Plasma endothelin levels in patients with cirrhosis and their relationships to the severity of cirrhosis and renal function. *J Hepatol* 1995;23:681–8.

21. Pinzani M, Milani S, DeFranco R, Grappone C, Caligiuri A,Gentilini A, Tosti-Guerra C, et al. Endothelin 1 is overexpressed in human cirrhotic liver and exerts multiple effects on activated hepatic stellate cells. *Gastroenterology* 1996;110:534–48.

22. Bezie Y, Mesnard L, Longrois D, Samson F, Perret C, MercadierJJ, Laurent S. Interactions between endothelin-1 and atrial natriuretic peptide influence cultured chick cardiac myocyte contractility. *Eur J Pharmacol* 1996;311:241–8.

23. Hirata Y, Emori T, Eguchi S, Kanno K, Imai T, Ohta K,Marumo F. Endothelin receptor subtype B mediates synthesis of nitric oxide by cultured bovine endothelial cells. *J Clin Invest* 1993;91:1367–71.

24. Cahill PA, Hou MC, Hendrickson R, Wang YN, Zhang S,Redmond EM, Sitz JV. Increased expression of endothelin receptors in the vasculature of portal hypertensive rats: role in splanchnic hemodynamics. *Hepatology* 1998;28:396–403.

25. Miller VM, Gutkowska J. Modulation of arterial endothelin-1 receptors following chronic increases in blood flow. *J Cardiovasc Pharmacol* 1992;20:15–8.

26. Newman P, Kakkar VV, Kanse SM. Modulation of endothelin receptor expression in human vascular smooth muscle cells by interleukin-1 beta. *FEBS Lett* 1995;363:161–4.

27. Li H, Elton TS, Chen YF, Oparil S. Increased endothelin receptor gene expression in hypoxic rat lung. *Am J Physiol* 1994;266:553–60.

28. Arguedas MR, Drake BB, Kapoop A, Fallon MB. Carboxyhemoglobin levels in cirrhotic patients with and without hepatopulmonary syndrome. *Gastroenterology* 2005;128:328–33.

29. Morse D, Choi AM. Heme oxygenase-1: the "emerging molecule" has arrived. *Am J Respir Cell Mol Biol* 2002;27:8–16.

30. Carter EP, Hartsfield CL, Miyazono M, Jakkula M, Morris KG Jr, McMurtry IF. Regulation of heme oxygenase-1 by nitric oxide during hepatopulmonary syndrome. *Am J Physiol Lung Cell Mol Physiol* 2002;283:346–53.

31. Zhang J, Ling Y, Luo B, Tang L, Ryter S, Stockard C, Grizzle W, et al. Analysis of pulmonary heme oxygenasae-1 and nitric oxide synthase alternations in experimental hepatopulmonary syndrome. *Gastroenterology* 2003;125:1441–51.

32. Luo B, Liu L, Tang L, Zhang J, Ling Y, Fallon MB. ET-1 and TNF-alpha in HPS: analysis in prehepatic portal hypertension and biliary and nonbiliary cirrhosis in rats. *Am J Physiol Gastrointest Liver Physiol* 2004;286:294–303.

33. McAdams HP, Erasmus J, Crockett R, Mitchell J, Godwin JD,McDermott VG. The hepatopulmonary syndrome: radiologic findings in 10 patients. *AJR Am J Roentgenol* 1996;166:1379–85.

34. Gomex FP, Martinex-Palli G, Barbera JA, Roca J, Navasa M,Rodriguez-Roisin R. Gas exchange mechanism of Orthodeoxia in hepatopulmonary syndrome. *Hepatology* 2004;40:660–6.

35. Martinex GP, Barbera JA, Visa J, Rimola A, Pare JC, Roca J,Navasa M, et al. Hepatopulmonary syndrome in candidates for liver transplantation. *J Hepatol* 2001;34:651–7.

36. Krowka MJ, Cortese DA. Pulmonary aspects of liver disease and liver transplantation. *Clin Chest Med* 1989;10:593–616.

37. Vedrinne JM, Duperret S, Bizollon T, Magnin C, Motin J,Trepo C, Ducerf C. Comparison of transesophageal and transthoracic contrast echocardiography for detection of an intrapulmonary shunt in liver disease. *Chest* 1997;111: 1236–40.

38. Hopkins WE, Waggoner BA, Barzilai B. Frequency and significance of intrapulmonary right-to-left shunting in endstage epatic disease. *Am J Cardiol* 1992;70:516–9.

39. Krowka MJ, Porayko MK, Plevak DJ, Pappas SC, Steers JL,Krom RA, Wiesner RH. Hepatopulmonary syndrome with progressive hypoxemia as an indication for liver transplantation: case reports and literature review. *Mayo Clin Proc* 1997; 72:44–53.

40. Soderman C, Juhlin-Dannfelt A, Lagerstrand L, Eriksson LS.Ventilation-perfusion relationships and central haemodynamics in patients with cirrhosis. Effects of a somatostatin analogue. *J Hepatol* 1994;21:52–7.

41. Schenk P, Schoniger-Hekele M, Fuhrmann V, Madl C,Silberhumer G, Muller C. Prognostic significance of the hepatopulmonary syndrome in patients with cirrhosis. *Gastroenterology* 2003;125:1042–52.

42. Battaglia SE, Pretto JJ, Irving LB, Jones RM, Angus PW.Resolution of gas exchange abnormalities and intrapulmonary shunting following liver transplantation. *Hepatology* 1997;25: 1228–32.

43. Taille C, Cadranel J, Bellocq A, Thabut G, Soubrane O,Durand F, Ichai P, et al. Liver transplantation for hepatopulmonary syndrome: a ten-year experience in Paris, France. *Transplantation* 2003;79:1482–9.

44. Krowka MJ. Hepatopulmonary syndrome: recent literature (1997 to 1999) and implications for liver transplantation.*Liver Transpl* 2000;6:31–5.

45. Kaspar MD, Ramsay MA, Shuey CB Jr, Levy MF, Klintmalm GG. Severe pulmonary hypertension and amelioration of hepatopulmonary syndrome after liver transplantation. *LiverTranspl Surg* 1998;4:177–9.

46. Martinex-Palli G, Barbera JA, Taura P, Cirera I, Visa J,Rodriguez-Roisin R. Severe portopulmonary hypertension after liver transplantation in a patient with preexisting hepatopulmonary syndrome. *J Hepatol* 1993;31:1075–9.

47. Abrams GA, Rose K, Fallon MB, McGuire BM, Bloomer JR, van Leeuwen DJ, Tutton T, et al. Hepatopulmonary syndrome and venous emboli causing intracerebral hemorrhages after liver transplantation: a case report. *Transplantation* 1999;68:

48. H.S. Hira, Jaya Kumar, S.K. Tyagi et al A Study of Hepatopulmonary Syndrome Among Patients of Cirrhosis of Liver and Portal Hypertension *Indian J Chest Dis Allied Sci 2003; 45 : 165-171*

49. Binay K De et al Clinical and haemodynamic aspects of hepatopulmonary syndrome in Indian patients with cirrhosis Volume 15 Issue 4 Page 412-416, April 2000

50. Anand AC, Mukherjee D, Rao KS, Seth AK Hepatopulmonary syndrome: prevalence and clinical profile. Indian journal of gastroenterology Year : 2001 /Volume : 20 Issue : 1 Page : 24-7

51. P Schenk[1], V Fuhrmann[1], C Madl[1], G Funk Hepatopulmonary syndrome: prevalence and predictive value of various cut offs for arterial oxygenation and their clinical consequences *Gut* 2002;51:853-859

52. Mimidis KP, Karatza C, S Prevalence of intrapulmonary vascular dilatations in normoxaemic patients with early liver cirrhosis. Scand J Gastroenterol 1998 Sep; 33(9) :988-92

53. Culafić Dj, Perisić M, Rebić P. Hepatopulmonary syndrome in liver cirrhosis Srp Arh Celok Lek. 2000 Jul-Aug;128(7-8):271-5.

54. Sarin et al prevalence and hemodynamic profile of Hepatopulmonary syndrome Indian journal of gastroenterology 2006 vol

55. Sood N, Sood A, Intrapulmonary vascular dilatation in portal hypertension due to cirrhosis of liver. Indian J Gastroenterol. 2001 Jan-Feb; 20(1):22-3.

56. Amir Houshang Mohammad Alizadeh, Seyed Reza Fatemi Clinical features of hepatopulmonary syndrome in cirrhotic patients. World J Gastroenterol 2006; 12(12): 1954-1956.

57. M.Bahtoei, M.D. Heptopulmonary syndrome shiraz E- medical journal ,October 2002, Vol. 3, No. 4

APPENDIX I - APPROVAL FROM ETHICAL COMMITTEE

Appendix I- Approval from Ethical Committee

K. Dis.No.1221/E4/1/2007. Govt. Rajaji Hospital,
Madurai – 625 020. Dt. 15.03.2007.

MANAGEMENT AND PROGRESS

Sub: Establishment – Govt. Rajaji Hospital, Madurai – Ethical Committee Projects approved by the Committee – Intimation – Sent – Reg.

The Ethical Committee of the Govt. Rajaji Hospital, Madurai was held at 12.30 pm. on 15.03.2007 at the Dean's Chamber, Govt. Rajaji Hospital, Madurai, and the following Projects were approved unanimously by the Committee Members.

S.No.	Name of the Student	Name of the Project approved
01)	Dr. D. BASKARAN, PG IN Paediatric Surgery.	The efficacy and safety of topical application of collagen for the treatment of Omphalocele.
02)	Dr. P. Kannan, DM PG in Cardiology.	Echo Cardiographic evaluation of HIV infected persons.
03)	Dr. R. Sankar, MD PG in General Medicine	Prevalence of Hepato pulmonary syndrome in chronic liver disease.
04)	Dr.P. Ramanathan, MD PG in General Medicine.	Serum Uric acid – an independent risk factor in acute non-embolic ischemic stroke.

Please note that the investigator should adhere the following:-

01) She/He should get a detailed informed consent from the patients/participants and maintain confidentially.
02) She/He should carry out the work without detrimental to regular activities as well as without extra expenditure to the Institution or Government.
03) She/He should inform the Institution Ethical Committee in case of any change of study procedure site and investigation or guide.
04) She/He should not deviate for the area of the work for which applied for Ethical clearance.
05) She/He should inform the IEC immediately, in case of any adverse events or serious adverse reactions.
06) She/He should abide to the rules and regulations of the Institution.
07) She/He should complete the work within the specific period and apply for, if any extension of time is required, She should apply for permission again and do the work.
08) She/He should submit the summary of the work to the Ethical Committee on completion of the work.
09) She/He should not claim any funds from the Institution while doing the work or on completion.
10) She/He should understand that the members of IEC have the right to monitor the work with prior intimation.

16/3/07

Dean/Chairman,
Ethical Committee, Govt. Rajaji Hospital, Madurai.

16/3/07

To
The above Members through the Concerned HODs.

1) Thro. prof + HOD of Paediatric Surgery
2) Thro prof + HOD of Cardiology
3) Thro prof + HOD of General Medicine

} GRH, Madurai

forwarded
Kalin
16/3/07

PROFESSOR AND HEAD
DEPARTMENT OF MEDICINE
MADURAI MEDICAL COLLEGE
MADURAI-625 020.

APPENDIX II – PRO FORMA

APPENDIX II

PRO FORMA

Case No:
Name:
Age:
Sex:
IP No:
Address: (rural/urban)
Occupation: (agricultural/nonagricultural)
Duration :

H/o present illness:

1. Abdominal distention
2. Abdominal pain
3. Jaundice
4. Hemetemesis
5. Melena
6. Fever
7. Dyspnea, Platypnea
8. Altered sensorium

Past History

Jaundice, blood transfusion,surgery, chronic lung disease, RHD/IHD, Tuberculosis, DM,HT

Personal History

Alcoholic-type ,quantity,duration, smoker

General examination

Consciousness, orientation, anemia, cyanosis, clubbing, pedal edema, lymphadenopathy

Signs of liver cell failure – jaundice, spidernaevi, gynecomastia, alopecia

Vitals:

- Pulse rate.
- BP.
- Respiratory rate.
- Weight.
- Temperature.

Systemic examination:

- CVS
- RS
- ABDOMEN
- CNS

Investigations:

- ◊ Hb, TC, DC.
- ◊ Urine examination
- ◊ Blood grouping and typing.
- ◊ Urea, creatinine and electrolytes
- ◊ Liver function tests
- ◊ Viral markers
- ◊ Chest Xray
- ◊ Ultrasound Abdomen
- ◊ OGD
- ◊ Contrast enhanced echo
- ◊ Arterial Blood Gas analysis

Child pugh score

APPENDIX III - MASTER CHART

S.No.	Name	Age	Sex	Alcoholic	HBs Ag	Anti Hcv Ab	Dyspnea	Platypnea	Cyanosis	Clubbing	Spider naevi	Child's Classification	Contrast Echo	PaO2mmHg	PaO2 mm Hg	P(A-a)O2 gradient
1	Alexander	38	1	2	1	2	2	2	1	1	1	B	Positive	48.2	< 80	58.9
2	A. Ramakrishnan	47	1	2	2	2	1	2	2	2	2	A	Negative	78	< 80	33
3	Mariappan	45	1	2	2	2	2	2	2	2	2	B	Positive	82.8	80-90	25.2
4	Chitrai Thirunal	58	1	1	2	2	1	2	2	2	2	C	Positive	95.7	> 90	15.5
5	Haseena begam	45	2	2	2	2	1	2	2	2	2	A	Negative	88.3	80-90	23.7
6	Srinivasan	44	1	1	2	2	1	2	2	2	2	C	Negative	87.8	80-90	23
7	Rayanathar	53	1	2	2	2	2	2	2	2	2	B	Negative	91.5	> 90	17.2
8	Dhanabalan	47	1	1	2	2	2	2	2	2	2	B	Negative	99.2	> 90	10.5
9	Ayesa beevi	65	2	2	2	2	2	2	2	2	2	B	Positive	103.4	> 90	7
10	Manoharan	52	1	1	2	2	1	1	2	2	2	A	Negative	98.3	> 90	11.8
11	Venkatakrishnan	60	1	2	2	2	1	2	2	2	2	B	Negative	72.2	< 80	0
12	Santhana lakshmi	45	2	2	2	2	2	2	2	2	2	B	Negative	93.9	> 90	0
13	Cholalingam	55	1	2	2	2	2	2	2	2	2	B	Negative	101.1	> 90	7.2
14	Somasundaram	73	1	2	2	2	2	2	2	2	2	B	Positive	110.9	> 90	0
15	Ramesh	40	1	1	2	2	2	2	2	2	2	B	Positive	87.3	80-90	28.3
16	Sivashankar	42	1	2	1	2	2	2	2	2	2	B	Positive	83.1	80-90	31.6
17	Balasaraswathy	54	2	2	2	1	2	2	2	2	2	B	Positive	101	> 90	8
18	Manoharan	49	1	1	2	2	1	2	2	2	2	B	Positive	100.9	> 90	12.2
19	Xavier	58	1	1	2	2	1	2	2	1	2	B	Negative	63.6	< 80	56
20	Venkatesan	78	1	2	2	2	2	2	2	2	2	A	Negative	94.1	> 90	21.4
21	Sriramabu	62	1	1	2	2	2	2	2	2	2	B	Positive	93.5	> 90	130
22	Arumugum	59	1	2	2	1	1	2	2	2	2	B	Negative	112.6	> 90	7.8
23	Selva natarajar	45	1	2	2	1	1	2	2	2	2	B	Negative	130.2	> 90	0

24	Mohan Rajam	41	1	2	2	2	2	2	2	2	2	A	Negative	110.5	> 90	0
25	Periyasamy	66	1	2	2	2	1	2	2	2	2	A	Negative	104.4	> 90	9.5
26	Rajendrar	47	1	1	2	2	2	2	2	1	2	A	Positive	99.2	> 90	11.9
27	Kanchana	40	2	2	2	2	1	2	2	2	2	A	Negative	97.9	> 90	12.7
28	Somasundaes	69	1	1	2	2	1	2	2	2	2	B	Negative	69.1	< 80	42.5
29	Kamal nisha	40	2	2	2	2	2	2	2	2	2	A	Positive	98.7	> 90	56.1
30	Cauvery	71	2	2	2	2	1	2	2	2	2	A	Positive	90.5	> 90	27.1
31	Veeramohan	47	1	2	2	2	2	2	2	2	2	B	Negative	84.3	80-90	27.6
32	Antony dass	51	1	2	2	2	1	2	2	2	2	B	Positive	96.5	> 90	20.4
33	Rajendran	40	1	1	2	2	1	2	2	2	2	B	Negative	88.8	80-90	565.4
34	Nayalakshmi	56	2	2	2	2	2	2	2	2	2	B	Negative	93.3	> 90	16.7
35	Vijayaragavan	65	1	2	2	2	1	2	2	2	2	C	Negative	113	> 90	6.1
36	Suriyakumar	45	1	1	2	2	2	2	2	2	2	A	Negative	91.9	> 90	28.7
37	Elango	53	1	1	2	2	1	2	2	1	2	B	Positive	94	> 90	301.2
38	Pandian	64	1	1	2	2	1	1	2	1	2	C	Positive	77.4	< 80	32.4
39	Andalagar	38	1	1	2	2	1	2	1	1	1	C	Positive	64.4	< 80	13
40	Muthuraman	45	1	1	2	2	2	2	2	1	2	B	Positive	81.3	80-90	32.9
41	Alagarsamy	59	1	Oce	2	2	2	2	2	1	2	A	Positive	115.3	> 90	5
42	Chellammal	55	2		2	1	1	2	2	2	2	B	Positive	93	> 90	22.7
43	James mary	62	2	2	2	2	2	2	2	2	2	A	Negative	85.8	80-90	22.9
44	Manikandan	34	1	1	1	2	2	2	2	2	2	B	Negative	106.3	> 90	0
45	Eanappan	35	1	1	2	2	2	2	2	2	2	B	Negative	68.6	< 80	549
46	Kasthuri	55	2	2	2	2	2	2	2	2	2	A	Negative	104.3	> 90	11.3
47	Rajapandi	48	1	1	2	2	1	2	2	2	2	A	Negative	85.6	80-90	20
48	Narayanan	67	1	1	2	2	2	2	2	2	2	A	Negative	49.1	< 80	60.2
49	Mayilshakti	55	2	2	2	2	2	2	2	2	2	A	Negative	78.3	< 80	31.5

50	Rajamannar	65	1	2	2	2	2	2	2	2	2	A	Negative	98.7	> 90	6.3
51	Saravanan	38	1	1	2	2	2	2	2	2	2	C	Negative	98.5	> 90	19.2
52	Ramasamy	45	1	2	1	2	2	2	2	2	2	B	Positive	95.4	> 90	15.7
53	Muthummal	78	2	2	2	2	2	2	2	2	2	B	Negative	65.8	80-90	15.3
54	Arumugum	68	1	2	2	2	1	2	1	1	2	A	Positive	76.1	< 80	40.1
55	Meeneesvaran	24	1	2	2	2	2	2	2	2	2	A	Negative	100.3	> 90	0
56	Murugesan	40	1	1	2	2	2	2	2	2	2	B	Positive	100.1	> 90	12
57	Murugaboopathy	48	1	1	2	2	1	2	1	1	2	C	Positive	68.4	< 80	44.5
58	Syed sulaiman	52	1	1	2	2	2	2	2	2	2	C	Positive	64.8	< 80	55
59	Chokkalingam	67	1	1	2	2	1	2	1	1	2	B	Positive	56.2	< 80	21.6
60	Balakrishnan	56	1	2	2	2	2	2	2	2	2	B	Negative	102.6	> 90	8.7
61	Annadikanan	36	1	1	2	2	2	2	2	2	2	B	Negative	71.3	< 80	39.6
62	Gunasekaran	42	1	1	2	2	1	2	2	2	2	C	Negative	64.5	< 80	92.6
63	Durairaj	62	1	1	2	2	2	2	2	1	2	C	Positive	87.5	80-90	29.6
64	Dhanalakshmi	72	2	2	1	2	1	2	2	2	2	B	Positive	73.9	< 80	37.8
65	Arumugam	54	1	1	2	2	2	2	2	2	2	A	Negative	95.5	> 90	13.2
66	Gopal	60	1	1	2	2	1	2	2	2	2	A	Negative	90.9	> 90	17.4
67	Chellam	74	1	1	2	2	1	2	2	2	2	B	Negative	88.3	80-90	29.3
68	Murugesan	38	1	1	2	2	1	2	1	1	2	C	Positive	65.6	< 80	26.1
69	Krishnamoorthy	27	1	2	2	2	1	2	2	2	2	A	Positive	105.9	> 90	2.1
70	Muthiah	62	1	1	2	2	2	2	2	2	2	A	Negative	91.8	> 90	23
71	Jeyalakshmi	60	2	2	2	1	2	2	2	2	2	B	Positive	93.7	> 90	29.5
72	Lakshmi	50	2	2	1	1	2	2	2	2	2	B	Positive	82.2	80-90	533.3
73	Jeyasingam	64	1	1	2	2	2	2	2	2	2	A	Negative	96.7	> 90	29.5
	1 - Present			2- Absent												
	2- Sex Male			2- Sex Female												